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CLINICAL ARTICLE

Delay in Diagnosis and Its Effect on Clinical Outcome in High-grade Sarcoma of Bone: A Referral Oncological Centre Study

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Objective: To investigate delay in diagnosis by both patients and doctors, and to evaluate its effect on outcomes of high-grade sarcoma of bone in a single-referral oncological center.

Methods: Fifty-four patients with osteosarcoma, 29 with Ewing sarcoma and 19 with chondrosarcoma were enrolled in this retrospective study. Delay in diagnosis was defined as the period between initial clinical symptoms and histopathological diagnosis at our center. The delays were categorized as patient- or doctor-related. Short total delays were defined as <4 months; prolonged delays >4 months were assumed to have prognostic relevance.

Results: Total delay in diagnosis was 688.0 days in patients with chondrosarcoma, which is significantly longer than the 163.3 days for osteosarcoma ($P < 0.01$) and 160.2 days for Ewing sarcoma ($P < 0.01$). Most doctor-related delays were at the pre-hospital stage, occurring at the general practitioner (GP)'s office. However, prolonged total delays (≥4 months) did not result in lower survival rates. Five-year-overall survival rates were 67.0% for osteosarcoma, 49.0% for Ewing sarcoma and 60.9% for chondrosarcoma. Survival was significantly lower for patients with metastatic disease for all three types of sarcoma.

Conclusion: Prolonged delay in diagnosis does not result in lower survival. Metastatic disease has a pronounced effect on survival. Aggressive tumor behavior results in shorter delays. Minimizing GP-related delays could be achieved by adopting a lower threshold for obtaining plain radiographs at the pre-hospital stage.

Key words: Doctor-related delay; Patient-related delay; Sarcoma; Survival

Introduction

High-grade primary bone sarcomas are rare and aggressively invade soft tissue from bone. The most common high-grade bone sarcomas are osteosarcoma, Ewing sarcoma and chondrosarcoma. Because of their malignant nature and ability to metastasize, aggressive treatment is required[1]. The introduction of chemotherapy has dramatically improved survival of individuals with osteosarcoma and Ewing sarcoma[2–6]. While surgical and medical treatment options have also evolved since then, there has been no further remarkable improvement in survival rates[7–9]. Early diagnosis and treatment are still vital because local control is easier and may help prevent metastasis. Metastasis of high-grade sarcomas of bone greatly impacts survival[10,11]. A cooperative group of oncologists in the Netherlands, Stichting Oncologische Samenwerking (SONCOS), has issued a general guideline on timely diagnosis of cancer. Diagnosing bone tumors is notoriously difficult and sometimes time-consuming, as in most cases multidisciplinary diagnosis by local or nationwide musculoskeletal tumor committees like the Dutch Committee on Bone Tumors is necessary. Hence, in some cases it is impossible to meet these guidelines.

Only a few series regarding delay in diagnosis have been published[12–16]. Prolonged duration of symptoms is associated with larger tumor size and increased rate of metastasis, but not with inferior outcomes[12,17]. Reducing patients' associated delay seems difficult because of the low incidence of these diseases. Most general practitioner s (GPs)

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will only encounter a primary bone sarcoma a few times during their entire career, even though they deal with musculoskeletal complaints daily. Kim *et al.* demonstrated that doctor-related delays followed by inappropriate primary procedures significantly influence survival[18]. A detailed analysis of diagnostic delays may reveal new insights on how to improve awareness among patients and physicians.

The University Medical Center Groningen (UMCG), one of four accredited bone tumor centers in the Netherlands, provides regional coverage for the treatment of bone sarcomas, as shown in Fig. 1. In this study, we quantified and analyzed patient- and doctor-related delays and their effects on clinical outcomes in a large series of high-grade bone sarcomas with the aim of identifying new strategies for shortening delays.

Material and Methods

All cases were selected from a prospectively maintained bone tumor registry at UMCG. A minimum follow-up of 12 months was an inclusion criterion. All 102 consecutive patients with high-grade bone sarcoma diagnosed between October 2000 and October 2012 were included. They comprised 54 patients with osteosarcoma, 29 with Ewing sarcoma and 19 with intermediate or high-grade chondrosarcoma.

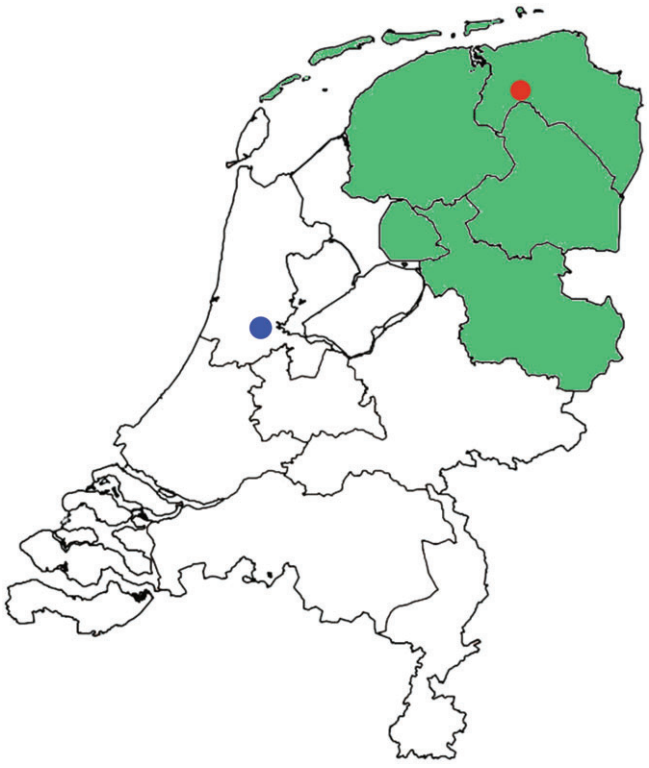

Fig. 1 Regional coverage for the treatment of bone sarcomas in the Netherlands. The capital of the Netherlands, Amsterdam, is marked in blue and the city of Groningen in red. The University Medical Center Groningen is located in Groningen and provides regional coverage, being the oncology center for the treatment of bone sarcomas in the northern provinces of the Netherlands. These northern provinces are marked in green.

Delays in diagnosis were calculated in days and categorized as patient-related or doctor-related. Patient-related delays were defined as the period between the initial symptom and first consultation with a GP, which is required for all Dutch patients prior to referral to a specialized service. GPs were asked to provide the date of the first entry in their medical records concerning tumor-related symptoms (swelling, daytime/night-time pain, loss of function, etc.). Doctor-related delays were further subdivided as follows: (i) between presentation to the GP's office and presentation to a primary hospital, defined as pre-hospital doctor-related delay; (ii) between presentation at a primary hospital and an oncology center, defined as primary clinic doctor-related delay; and (iii) between presentation to an oncology center and definitive histopathological diagnosis, defined as referral clinic doctor-related delay. The third group was further subdivided into two subgroups, ≤42 days and >42 days, according to the SONCOS guidelines. The date of presentation at each general primary hospital was obtained from the referral letters. When these were not available, the hospital was contacted with a request for the date of first presentation. Not every patient had been referred to a general secondary hospital; some had been referred directly to an oncology (referral) center or had presented to an emergency room. Short total delays were defined as <4 months; total delays longer than 4 months were assumed to have prognostic relevance based on expert opinion.

Local presenting symptoms comprised pain, swelling, pathological fracture and/or loss of function. The presence of systemic symptoms (fatigue, loss of appetite, weight loss or fever) was recorded separately.

The primary outcome measure was the effect of delay (patient- or doctor-related) on oncological outcomes. The secondary aims were to assess patients' symptoms in and determine whether outcomes were is affected by transgression of the 6-week rule. Statistical analysis was performed using SPSS statistics 20 for Windows. Normality was tested using the Shapiro–Wilk test. Survival analysis was performed separately for each pathological type of sarcoma using Kaplan–Meier survival curves. The impact of delay in diagnosis on joint salvage rate and local recurrence was also investigated using binary logistic regression analysis.

Results

In all, 102 patients, 57 of whom were male and 45 female, were enrolled in this study. The mean age at presentation was 30.0 years (range, 5–89 years). The subjects were categorized according to pathological diagnosis: 54 had osteosarcomas, 29 Ewing sarcoma and 19 chondrosarcoma. Clinicopathological characteristics according to pathological diagnosis are shown in Table 1.

TABLE 1 Clinicopathological characteristics according to sarcoma type

Characteristic	Osteosarcoma (*n* = 54)	Ewing sarcoma (*n* = 29)	Chondrosarcoma (*n* = 19)
Age at primary therapy (years, mean [range])	28.9 (8–86)	17.4 (5–56)	52.4 (21–89)
Sex (cases [%])			
Male	30 (55.6)	19 (65.5)	8 (42.1)
Female	24 (44.4)	10 (34.5)	11 (57.9)
Location (cases [%])			
Long bones	50 (92.6)	10 (34.5)	8 (42.1)
Axial skeleton	4 (7.4)	18 (62.1)	7 (36.8)
Other	—	1 (3.4)	4 (21.1)
Primary therapy (cases [%])			
Surgical excision	50 (92.6)	16 (55.2)	19 (100)
Chemotherapy/radiotherapy	4 (7.4)	13 (44.8)	—
Wide excision (cases [%])	46 (92.0)	9 (56.3)	16 (84.2)
Additional therapy (cases [%])			
(Neo-) adjuvant chemotherapy	44 (81.5)	27 (93.1)	—
Radiotherapy	10 (18.5)	22 (75.9)	3 (15.8)
Status after primary therapy (cases [%])			
Disease-free	37 (68.5)	15 (51.7)	15 (78.9)
Non-radical resection	3 (5.6)	3 (10.3)	2 (10.5)
Unresectable lesion	1 (1.9)	—	—
Metastatic disease	13 (24.1)	11 (37.9)	2 (10.5)
Follow-up (months, mean [SD])	54.9 (42.8)	39.2 (31.2)	54.6 (35.8)
Current status (cases [%])			
Continuously disease-free	24 (44.4)	11 (37.9)	10 (52.6)
Alive with disease	2 (3.7)	1 (3.4)	1 (5.3)
No evidence of disease	8 (14.8)	4 (13.8)	1 (5.3)
Dead of disease	18 (33.3)	13 (44.8)	6 (31.6)
Dead of other disease	2 (3.7)	—	1 (5.3)

SD, standard deviation.

Clinical Characteristics

Osteosarcomas were located in the long bones in 50 patients (92.6%), the femur being the predominant site (31 patients, 57.4%). Pain was the most frequent symptom, being present in 44 patients (81.4%). Most Ewing sarcomas were located in the axial skeleton (18 patients, 62.1%) with the spine or ribs as the predominant site in nine patients (31.0%), followed by the pelvis in eight patients (27.6%). Ten patients (34.5%) presented with Ewing sarcoma in their long bones. Pain was the commonest symptom, being present in 20 patients (68.9%). Chondrosarcomas were most in the long bones (eight patients, 42.1%); the most frequent symptom was pain, which was present in 13 patients (68.4%). Six patients (11%) with osteosarcoma and 10 (34.5%) with Ewing sarcoma presented with systemic symptoms, whereas were none of the patients with chondrosarcoma had systemic symptoms.

Delays in Diagnosis

The mean delay in diagnosis is shown in Table 2 and Fig. 2. The mean total delay was 163.3 days (standard deviation [SD], 176.5 days) in patients with osteosarcoma, 160.2 days (SD, 193.7 days) in patients with Ewing sarcoma, and 688.0 days (SD, 678.4 days) in patients with chondrosarcoma, this mean total delay being significantly longer than that for osteosarcoma and Ewing sarcoma ($P < 0.01$). The mean patient-related delay for all types of sarcoma was 83.2 days (SD, 208.1 days), being 244.1 days for chondrosarcoma, which is somewhat longer than that for osteosarcoma (44.8 days, $P = 0.058$) and significantly longer than that for Ewing sarcoma (41.0 days, $P = 0.034$).

The mean overall doctor-related delay was 156.2 days (SD, 210.9 days). Mean doctor-related delay for chondrosarcoma was 332.3 days, which is significantly longer than for osteosarcoma (100.0 days, $P \leq 0.01$) and Ewing sarcoma (130.6 days, $P < 0.01$). Mean overall pre-hospital doctor-related delay was 101.5 days (SD, 189.7 days); data on this were unavailable for 14 cases (13.5%). The mean overall primary clinic doctor-related delay was 23.5 days (SD, 30.4 days), data being unavailable for 3.9% of cases. This delay was significantly longer for patients with chondrosarcoma (49.7 days) than for those with osteosarcoma (16.5 days; $P < 0.01$) or Ewing sarcoma (16.3 days; $P < 0.01$). The mean overall referral clinic doctor-related delay was 27.6 days (SD, 29.6 days), all data being available.

Outcomes

Metastatic disease was present at diagnosis in 24.1% of patients with osteosarcoma, 37.9% with Ewing sarcoma and 10.5% with chondrosarcoma. Surgical resection of the primary tumor was performed in 92.4% of patients with osteosarcoma and 55.2% with Ewing sarcoma; all patients with chondrosarcoma underwent surgical resection. There was no

TABLE 2 Delay in diagnosis (days, mean [standard deviation]) according to sarcoma type

Mean delay in days	Osteosarcoma (n = 54)	Ewing sarcoma (n = 29)	Chondrosarcoma (n = 19)
Total delay	163.3 (176.5)	160.2 (193.7)	688.0 (678.4)*
Patient-related delay	44.8 (41.8)	41.0 (40.5)	244.1 (433.5)*
Mean doctor-related delay	100.0 (94.6)	130.6 (217.6)	332.3 (312.7)*
Pre-hospital doctor-related delay	57.8 (56.1)	103.6 (223.8)	197.2 (291.9)
Primary clinic doctor-related delay	16.5 (21.3)	16.3 (21.3)	49.7 (43.6)*
Referral clinic doctor-related delay	26.6 (28.2)	24.5 (28.0)	34.9 (36.0)

*Significant difference ($P < 0.05$).

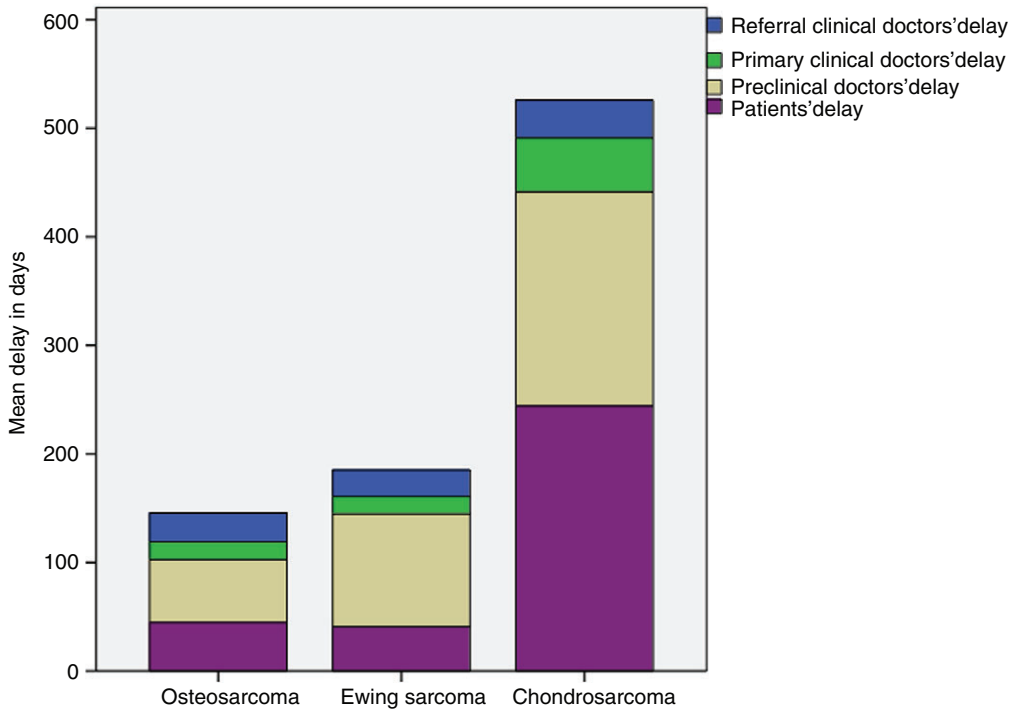

Fig. 2 Mean diagnostic delay in days.

association between length of delay and rate of limb salvage procedures. Overall, 16 patients with tumors in the axial skeleton underwent surgical excision, resulting in intralesional resections in 43.8% of them, compared with 9.4% of 60 patients with tumors in the long bones ($P < 0.01$). Adjuvant chemotherapy was given to 93.7% of patients with Ewing sarcoma. Local recurrence was diagnosed in 16 patients (15.7%), six of whom had osteosarcomas (11.1%), five Ewing sarcomas (17.2%) and five chondrosarcomas (26.3%). There was no association between length of delay and local recurrence rate for any single pathological type or overall. At the end of follow-up, 44.4% of patients with osteosarcoma, 37.9% with Ewing sarcoma and 52.6% with chondrosarcoma were continuously disease-free. After primary treatment, no evidence of disease was seen in 14.8% of subjects with osteosarcoma, 13.8% of those with Ewing sarcoma and 5.3% of those with chondrosarcoma. Patient mortality was highest for Ewing sarcoma; 44.8% of cases dying of disease.

Survival

Thirty-eight patients (37.3%) had a minimum follow-up of 5 years. The mean duration of follow-up in patients with osteosarcoma was 54.9 months (SD, 42.8 months) with a 5-year overall survival rate (60 months) of 67.0% (SD, 6.6 months). The mean duration of follow-up in patients with Ewing sarcoma was 39.2 months (SD, 31.2 months) with a 5-year overall survival rate (62 months) of 49.0% (SD, 11.1 months). The mean duration of follow-up in patients with chondrosarcoma was 54.6 months (SD, 35.8 months) with a 5-year overall survival rate (61 months) of 60.9% (SD, 13.0 months). Five-year overall survival curves are displayed in Fig. 3.

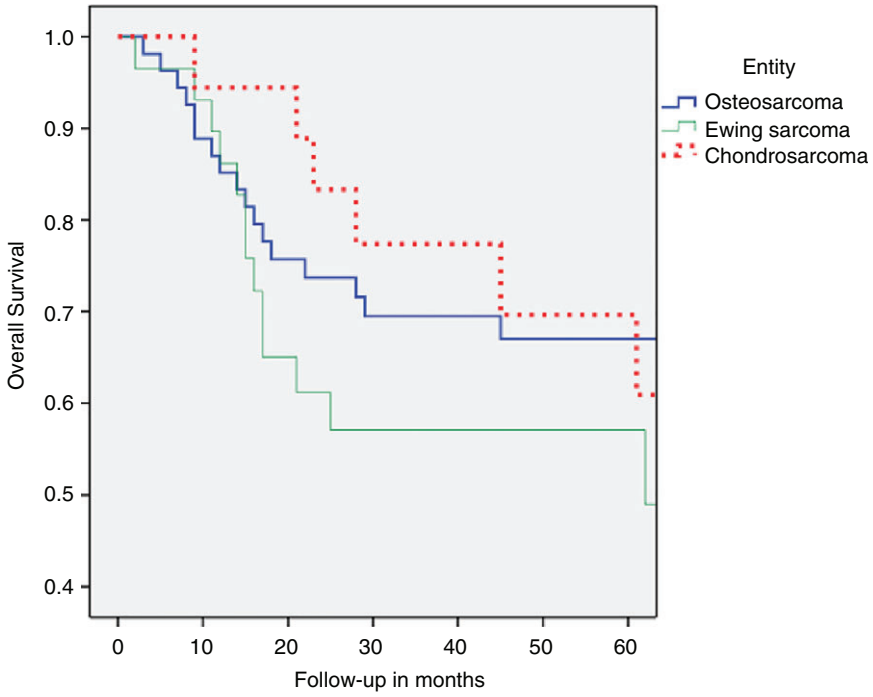

Fig. 3 Five-year-overall survival for high-grade sarcoma of bone according to sarcoma type.

Overall (all sarcoma types), 5-year-overall survival rates were significantly lower for patients with tumors in the axial skeleton (46.0%) than for those with long bone tumors (72.3%; $P = 0.016$). In patients with osteosarcoma, the 5-year-overall survival was significantly lower for tumors in the axial skeleton (25.0%) than for those in long bones (71.0%; $P = 0.026$). For Ewing sarcoma and chondrosarcoma, tumor location did not significantly impact 5-year-overall survival.

The 5-year-overall survival of patients with osteosarcoma was significantly lower after intralesional resection (25.0%) than after wide resection (77.3%; $P = 0.01$). Similarly, for Ewing sarcoma, the 5-year-overall survival was significantly lower after intralesional resection (42.9%) than after wide resection (71.1%; $P = 0.048$). The excision margin did not significantly impact 5-year-overall survival in subjects with chondrosarcoma.

Five-year-overall survival rates were significantly lower in patients with metastatic osteosarcoma (26.9%) than in patients who remained disease-free after resection (79.3%; $P < 0.01$). Survival of subjects with metastatic Ewing sarcoma was also significantly lower (36.4%) than for disease-free patients (72.7% after 62 months; $P < 0.01$). The 5-year overall survival rates of patients with chondrosarcoma and metastases was 50% compared 69.5% in patients who remained disease-free ($P < 0.01$).

The mean overall delay from presentation at UMCG to histological diagnosis for each sarcoma type was compared based on the SONCOS guidelines and it was found that the 5-year overall survival rate for osteosarcoma diagnosed in <42 days was 58.2%, as against 76.9% in patients diagnosed ≥42 days (not significant [NS]). The overall survival rate after 62 months for patients with Ewing sarcoma diagnosed in <42 days was 39.4%, compared to 80.0% of patients diagnosed ≥42 days (NS). The overall survival after 61 months for chondrosarcoma was 46.2% in patients diagnosed in <42 days and 83.3% in patients diagnosed ≥42 days (NS).

There were no significant differences in 5-year overall survival rates between total delay <4 months and a longer total delay for patients with osteosarcoma and Ewing sarcoma. There was no significant difference in overall survival rates between a total delay <4 months (two patients, 50% overall survival after 40 months) and a delay ≥4 months (17 patients, 63.6% overall survival after 61 months) for patients with chondrosarcoma. No significant differences were identified in metastatic disease rates after a total delay <4 months compared to a longer total delay for any of the three pathological types or for all subjects combined.

Discussion

Delay in diagnosis may have an adverse effect on oncologic outcomes. SONCOS guidelines state that diagnosis at an oncology center within 42 days minimizes negative effects on outcome. The purpose of this study was to investigate patient- and doctor-related delays and evaluate their effects on outcomes. High-grade bone sarcomas are rare neoplasms; 102 lesions were seen in our referral oncology center over 12 years. The present study provides a valuable addition to data of other published Dutch series on outcomes of high-grade bone sarcomas[19–22]. Furthermore, this report includes 8.3% of all patients with high-grade bone sarcomas who underwent orthopaedic oncological treatment in the Netherlands during that 12 years[23]. Because our study focused on the effect of delay in diagnosis, one of its limitations is that we did not include tumor size as a prognostic factor[24].

TABLE 3 Relevant published reports on delay in diagnosis of high-grade bone sarcomas

Authors	Years	Sarcoma type	Conclusion
Sneppen and Hansen[14]	1984	84 osteosarcomas 40 Ewing sarcomas	No association between delay and survival
Wurtz *et al.*[25]	1999	68 pelvic chondrosarcomas	No association between delay and survival
Widhe and Widhe[15]	2000	102 osteosarcomas 47 Ewing sarcomas	Doctor-related delay significantly longer for Ewing sarcoma
Bacci *et al.*[26]	2000	965 high-grade osteosarcomas	Aggressive tumor behavior results in shorter delay
Kim *et al.*[18]	2009	26 osteosarcomas	Doctor-related delay superimposed on an inappropriate primary procedure has a detrimental effect on survival
Pan *et al.*[13]	2010	30 knee-region osteosarcomas	Total delay in diagnosis 17 weeks
Goedhart *et al.* (current study)	2016	54 osteosarcomas 29 Ewing sarcomas 19 chondrosarcomas	Longer delay in patients with chondrosarcoma, no effect on outcome

There are few relevant published reports, as shown in Table 3. Bacci *et al.* reported a shorter delay in patients with metastatic osteosarcomas than in those with localized disease[12]. They concluded that aggressive tumor behavior results in shorter delays. This conclusion is in accordance with our results, since patients with chondrosarcoma had significantly longer delays in diagnosis than those with osteosarcoma and Ewing sarcoma. However, the long delay in diagnosis of intermediate and high-grade chondrosarcoma did not result in lower survival rates. We believe that this can be explained by less aggressive tumor behavior, absence of systemic symptoms and the inclusion of intermediate-grade chondrosarcomas. However, it is important to recognize that chondrosarcoma can dedifferentiate and that this is associated with poor survival.

Sneppen and Hansen defined treatment delay as the time from the first symptom until presentation at an oncology center[14]. Their mean treatment delay was 6.4 months for osteosarcoma and 9.6 months for Ewing sarcoma, which is longer than our series, in which there was a treatment delay of 3.9 months for osteosarcoma and 5.3 months for Ewing sarcoma. Comparison between the Bacci study and our own is difficult because referral patterns and accuracy have evolved over the past 30 years.

Primary orthopaedic hospitals in the Netherlands follow the guidelines on bone tumors, which specify that biopsy and treatment should be performed in an oncology referral center. Although diagnostic delay at an oncology center makes up only a small slice of the total delay, it is the most visible type of delay. According to SONCOS, the acceptable referral clinic doctor-related delay for a Dutch oncological center to diagnose a neoplasm and start treatment is 42 days[27]. In this study, the referral clinic doctor-related delay from presentation to diagnosis was 27.6 days and thus within our national standards. For high-grade chondrosarcoma it was 34.9 days. Because these tumors often present in the pelvis and may therefore be difficult to access for biopsy, multiple biopsies may be performed before a definitive diagnosis is made. Delay in diagnosis is also associated with other clinical variables; Kim *et al.* found that misdiagnosis and inappropriate treatment resulted in inferior outcomes in subjects with osteosarcoma[18]. This is in accordance with our study, in which we found significantly lower survival rates in patients with osteosarcoma and Ewing sarcoma after intralesional surgical resection. Furthermore, intralesional surgical resection occurred more often with tumors located in the axial skeleton. Location of a tumor in the axial skeleton is also associated with lower survival rates.

According to our data, diagnosis after 42 days of high-grade bone sarcomas does not result in lower survival; neither do total delays exceeding 4 months. And yet, paradoxically, metastatic disease after primary resection is associated with significantly lower survival rates. This discrepancy may be explained by the fact that aggressive tumor behavior results in early clinical symptoms, thereby facilitating a timely diagnosis. Our findings imply that tumor location and resectability have more influence on survival than delay in diagnosis in patients with osteosarcoma and Ewing sarcoma.

Tumor location and resectability, metastatic disease at diagnosis, response to chemotherapy and local recurrence are known prognostic factors for osteosarcoma and Ewing sarcoma according to published reports[8,26,28–34].

Most of the diagnostic delay occurred in the prehospital setting at the GP's office. We realize that is very difficult for GPs to recognize a bone malignancy because they generally only encounter one or two primary bone sarcomas in their entire careers. Pain was the most common symptom in our study and in other reports[14,15]. Therefore GPs should have a low-threshold for requesting plain radiographs in patients with pain and no history of trauma; such a policy would likely decrease mean doctor-related delay by accelerating referral to an oncology center. Persistent pain for more than 6 weeks is a red flag and an indication for a radiograph.

In conclusion, this study provides valuable insight into diagnostic delay patterns for high-grade bone sarcomas in the Netherlands. Prolonged delay in diagnosis of high-grade sarcomas of the bone does not result in lower survival. The SONCOS guidelines for diagnosing neoplasms are easily met, but do not seem clinically relevant to high-grade bone sarcomas. Persistent pain for more than 6 weeks in the prehospital (GP) setting is an indication for a radiograph.

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